CLAIMS

What is claimed is:

1. A method of separating a target oligonucleotide from an impurity, in a mixture comprising said target oligonucleotide and said impurity, using a titratable anion exchange composition, comprising the steps:

a) binding said target oligonucleotide to said titratable anion exchange composition;

b) passing a solution through said titratable anion exchange composition with target oligonucleotide bound thereon, wherein said solution increases in pH over time; and

c) eluting said target oligonucleotide, wherein said impurity elutes at a different pH than said target oligonucleotide.

2. The method of claim 1 wherein said titratable anion exchange composition comprises a primary amine, a secondary amine or a tertiary amine.

3. The method of claim 1 or claim 2, wherein said titratable anion exchange composition comprises polyethyleneimine, polyimizadole, polyhistidine or polylysine.

4. The method of any preceding claim, wherein said solution in b) is substantially free of metal salts.

5. A method according to any preceding claim, wherein the solution in b) does not substantially increase its salt concentration over time.

6. The method of any preceding claim, wherein said titratable anion exchange composition is conjugated to a support.

7. The method of claim 6, wherein said support is a synthetic polymer.

8. The method of claim 7, wherein said synthetic polymer is selected from the group consisting of silica gel, a polysaccharide, a styrene-divinyl benzene copolymer, a polyethylene, a polypropylene, a polyacrylic and an agarose.

9. The method of claim 8, wherein said titratable anion exchange composition is polyethyleneimine-derivatized silica gel or a polyethyleneimine-derivatised styrene-divinyl benzene copolymer.

10. The method of any preceding claim, wherein said target oligonucleotide is a synthetic oligonucleotide.

11. The method of Claim 10, wherein said synthetic oligonucleotide is selected from the group consisting of a phosphorothioate, a phosphorodithioate, a methyl phosphonate and a phosphoramidate.

12. The method of any preceding claim, wherein binding of said target oligonucleotide with said titratable anion exchange composition occurs at a pH between 5 and 8.

13. The method of any preceding claim, wherein said solution in b) increases in pH in a linear manner over time.

14. The method of any preceding claim, wherein said solution in b) increases from a pH of about 8 to a pH of about 11.

15. The method of any preceding claim, wherein said solution in b) comprises one or more of NH_4HCO_3 and/or NH_4OH.

16. The method of any preceding claim, wherein said target oligonucleotide has a length from about 8 to about 40 nucleotides.

17. The method of any preceding claim, wherein said impurity is one or more oligonucleotides having a shorter length than said target oligonucleotide, and wherein said impurity elutes at a lower pH than said target oligonucleotide.

18. The method of claim 17, wherein said impurity is one or more failure sequences.

19. The method of any one of claims 1 to 16, wherein said impurity is a metal salt.

20. The method of any preceding claim, wherein said target oligonucleotide is 5'-O-protected.

21. The method of claim 20, wherein said target oligonucleotide is 5'-O-trityl, preferably 5'-O-dimethoxy-trityl, protected.

22. The method of claim 21, further comprising a step of passing through said titratable anion exchange composition a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from said target oligonucleotide prior to eluting said target oligonucleotide.

23. The method of claim 22 wherein said acidic solution comprises aqueous acetic acid.

24. The method of any preceding claim, wherein said solution in b) has a volume which is less than the volume of the mixture comprising said target oligonucleotide and impurity, thereby increasing the concentration of said target oligonucleotide.

25. The method of any preceding claim, further comprising one or more washing steps prior to eluting said target oligonucleotide.